PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 498 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/50089	International filing date *(day/month/year)* 02.04.2003	Priority date *(day/month/year)* 03.04.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/52		
Applicant APPLIED RESEARCH SYSTEMS ARS HOLDING N.V. ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.09.2003	20.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Schönwasser, D Telephone No. +49 30 25901-318

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50089

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-42 as originally filed

Claims, Numbers

1-33 received on 27.11.2003 with letter of 26.11.2003

Drawings, Sheets

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 2,4,9

   because:

   ☒ the said international application, or the said claims Nos. 19-21,30 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 2,4 at least partially are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 9

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4,19,20,25-29
	No:	Claims	5-8,10-18,21-24,30-33
Inventive step (IS)	Yes:	Claims	1-4,19,20,25-29
	No:	Claims	5-8,10-18,21-24,30-33
Industrial applicability (IA)	Yes:	Claims	1-8,10-18,22-29,31-33
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

As outlined in the International Search Report (ISR), the search for claims 2 and 4 (previously claim 5) has been restricted to subject-matter which appeared to be detailed in the description (see ISR, PCT/ISA form 210), while no search could be carried out for subject-matter of claim 9.
As a consequence, the present International Preliminary Examination Report only relates to the searched subject-matter of those claims.

Claims 19-21 and 30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The applicant's comments filed with the letter of 26.11.2003 have been considered.

Reference is made to the following documents:

D1: WO 95 21915 A (UNIV LELAND STANFORD JUNIOR (US)) 17 August 1995 (1995-08-17) cited in the application

D2: DATABASE GSP [Online] 12 February 2001 (2001-02-12) ROSEN C.A. ET AL.: 'Human sereted protein sequence encoded by gene 39 SEQ ID NO:99' Database accession no. AAB44733 XP002211958 -& WO 00 58494 A (HUMAN GENOME SCIENCE INC.) 5 October 2000 (2000-10-05)

1. Amendments

The amendments filed with the letter dated 26.11.2003 do not add any subject-matter which extends beyond the contents of the application as filed and thus fulfil the requirements set out in Art. 19(2) and 34(2)(b), PCT.

2. Novelty, inventive step and industrial applicability (Art. 33(2)(3)(4), PCT)

2.1 The application relates to OX40 receptor (OX40R) binding agents, which are fragments of the extracellular region of human full-length OX40 ligand (OX40L) and to the use of said OX40R binding agents for antagonising the binding of full-length OX40L to its receptor as well as for treating of autoimmune diseases, inflammations and infections. Nucleic acids encoding said OX40L fragments, fusion proteins of OX40L fragments, OX40L fragments immobilized on a support and labelled OX40L fragments are also claimed.

2.2 D1 discloses binding agents for OX40R (here named "ACT-4-L", which is an alternative name for OX40L according to page 1, lines 10-11 of the application), wherein said binding agents comprise at least 5 amino acids of the extracellular region of OX40L (page 6, line 19-page 7, line 6; page 38, line 19-page 39, line 18). The use of these binding agents as competitive inhibitors of the binding between OX40L and OX40R and for treating autoimmune diseases, inflammations and infections is also discussed (page 38, line 19-page 39, line 18; page 69, line 1-page 70, line 24; page 75, line 12-page 77, line 17). Further, fusion proteins of OX40L fragments, OX40L fragments immobilized on a support and labelled OX40L fragments are mentioned (page 7, lines 8-14; page 63, line 11-page 63, line 3).

Although the claimed OX40R binding agents fall within the range of OX40R binding agents already known from D1 (here: peptides of 5 amino acids or more from the extracellular region of OX40L) and serve the same purpose, the selected subrange of OX40R binding agents of the present application is considered

a) narrow as compared to the range disclosed in D1,

b) sufficiently far removed from the endpoints of the known range.

c) Further, it was demonstrated that the technical effect occurs in the claimed subrange of the present application, but not in the whole of the range known from D1 (purposive selection; see Fig. 5,6).

Hence, the disclosure of D1 is not detrimental to novelty and inventive step of subject-matter of claims 1-33 (Art. 33(2)(3), PCT).

2.3 D2 discloses a polypeptide (SEQ ID NO:99), which comprises the peptide as defined in SEQ ID NO:13 of the application, as well as the corresponding nucleic acid, a vector, a host cell, fusion proteins (p. 47, 5th line of the table; p. 104, l. 1-p. 107, l. 5; p. 113, l. 9-p. 121, l. 25; p. 181, l. 20-182, l. 19) methods for producing said peptide and pharmaceutical compositions comprising said peptide.

Since subject-matter of claims 5-8,10-18,21-24 and 30-33 relates to a peptide "comprising" the sequence corresponding to SEQ ID NO:13 and corresponding nucleic acids, vectors, host cells, cell lines, fusion proteins, methods for producing said peptide and pharmaceutical compositions comprising said peptide, said claims are not in accordance with the requirement of Art. 33(2)(3), PCT.

2.4 Please note that for the assessment of the present claims 19-21 and 30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Further Comments

3.1 The use of brackets in claims 1-3 and 5 leaves the reader in doubt as to whether the bracketed terms (here: SEQ ID NOs) are limiting features or preferred embodiments of the claimed subject-matter (Art. 6, PCT).

3.2 Claim 12 does not meet the requirements of Art. 6, PCT in that the matter for which protection is sought is not clearly defined. The expression "which allows the expression of..." cannot be considered a technical feature, but is a mere desideratum (Art. 6, PCT).

3.3 The present set of claims contains two "claims 19" and two "claims 28" (Art. 6, PCT).